## REMARKS

Introductory Comments:

Claims 1-26 and 29-47 were pending in the application. Claims 6, 8-11, 13-14 and 26 have been withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b) as drawn to a non-elected invention. Accordingly, claims 1-5, 7, 12, 15-25 and 29-47 are currently under consideration and were examined in the Office Action dated 13 August 2002. Applicants note with appreciation that the Office has withdrawn the following rejections: **(a)** the rejection of claims 27 and 28 under 35 U.S.C.§101; **(b)** the rejection of
claims 27 and 28 under 35 U.S.C. § 112, second paragraph; and **(c)** the rejection of claims 29-32 under 35 U.S.C. §112, first paragraph.

However, the following claim rejections have been maintained: **(1)** claims 1, 16 and 33-47 remain rejected under 35 U.S.C. §112, first paragraph, as nonenabled; **(2)** claims 1, 2, 7, 12, 15, 29, 33, 35, 37, 39, 41, 43, 46 and 47 remain rejected under 35 U.S.C. § 102(e) as unpatentable over US Patent No. 5,925,362 to Spitler et al. ("Spitler"); and **(3)** claims 1, 3-5, 17-25, 29-34, 36-38, 40, 42, 44 and 45 stand rejected under 35 U.S.C. §103(a) as unpatentable over Spitler in view of Fynan et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:11478-11482 ("Fynan"), Golding et al. (1994) *Am. J. Trop. Med. Hyg.* 50(4):33-40 ("Golding"), and Sedegah et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:9866-9870 ("Sedegah"). Applicants respectfully traverse these rejections for the following reasons.

The Rejection under 35 U.S.C. §112, first paragraph:

Claims 1, 16 and 33-47 remain rejected under 35 U.S.C. §112, first paragraph, as nonenabled. Initially, the Office correctly points out that applicants have elected a single species for the current examination, that is, DNA vaccine compositions containing a lipid adjuvant composition, and that the application contains a working example of this composition, wherein CEA-encoding DNA was administered with and without the monophosphoryl lipid A (MPL) adjuvant (Example 1).. The Office's position is that, although applicants' Example 1 shows a decrease in the ratio of CEA-specific IgG1 to IgG2a in mouse sera when compared to administration of the CEA plasmid alone, this does not enable the invention as claimed since "it is clear that applicants' data does not demonstrate a 'shift' from Th2 to Th1 since the overall ratio of IgG1 to IgG2a shows that the predominant isotype is IgG1 rather than IgG2a which indicates a Th2 type response" and "applicants' data therefore only demonstrates a decrease in the magnitude of the T helper response rather than an actual shift." Office Action at page 5. On this basis, the Office concludes "it would have required undue experimentation to practice the invention as claimed." Office Action at page 7. Applicants respectfully traverse.

The single issue at hand regarding the instant enablement rejection can be summarized as being a difference between the Office's and applicants' interpretation of the data from Example 1. Applicants submit that the significant shift in the IgG1/IgG2 ratio seen with all compositions where the MPL adjuvant was co-administered with the CEA antigen-encoding DNA demonstrates a shift from a predominantly Th2 response to a Th1 response. The Office submits that the data merely show a decrease in the magnitude of the T helper response. Applicants respectfully submit that the Office has come to the wrong conclusion for the following reasons.

It is well known in the art that antibody synthesis in almost all classes shows considerable dependence upon T-cooperation. In particular, synthesis of the entire IgG class is heavily influenced by the relevant T helper response. A reduction in the T helper response would therefore affect both IgG1 and IgG2 production, presumably decreasing production of both IgG isotypes in roughly the same order of magnitude. Accordingly, if the Office's position were correct and the only result of administering the MPL adjuvant was to reduce the T helper response without bringing about a Th2/Th1 shift, one would expect to see no change in the magnitude of the IgG1/IgG2 ratio, but rather an overall change in the frequency of the humoral response. In other words, identical decreases to both the numerator and the denominator of the ratio would not reduce the ratio, for example the magnitude of the two ratios: 30,000/1000 and 30/1 are identical, it is just that in the first ratio, the frequency of the observed event was greater. However, as demonstrated in Example 1, use of the MPL adjuvant shifted the ratio of IgG1 to IgG2 in all of the experimental groups. In one case, the shift was evidenced by a decrease that was five-fold, from 27.5/1 to 4.5/1. Applicants submit that this sort of shift cannot be explained by the Office's theory of general T helper reduction, that is, it is not simply a matter of generally disabling the T helper response, it is demonstration of a significant shift in the immune response where the immune response has been shifted from one IgG isotype to another.

With regard to the Office's argument that the overall ratio of IgG1 to IgG2 continues to show the predominant isotype as IgG1 "which indicates a Th2 response" (and therefore no shift), applicants note that the Office must be arguing that in order to have a Th1/Th2 shift, one must eliminate one of the two isotypes from participating in the immune response. Applicants submit that this is not the case. As disclosed and discussed numerous times throughout applicants' specification, an immune-shift adjuvant merely "shifts" the nature of the immune response from favoring one type of

response to another. It is not a matter of eliminating the entire IgG1 response, it is a matter of significantly increasing the IgG2a component of the overall immune response. This demonstrated increase in the IgG2a component of the immune response, applicants submit, is the result of a shift from a Th1-type response to a Th2-type response, not some sort of general disabling of the T helper response.

More particularly, it is well known in the art that the cytokine interferon-gamma (IFN-γ) selectively induces switching to IgG2a in mice, and that the cytokine interleukin 4 (IL-4) reduces IgG2a production.. The two best defined subsets of helper T cells are Th1 cells which secrete IL-2 and IFN-γ, and Th2 cells which secrete IL-4. Thus, the skilled artisan understands that, when two compositions are compared head-to-head and the difference between the two test compositions is the addition of an adjuvant, and there is a marked increase in the IgG2a response as a result of the addition of the adjuvant, there has been a Th1/Th2 switch.

For all of the foregoing reasons, then, the rejection of claims 1, 16 and 33-47 under 35 U.S.C. §112, first paragraph, is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

The Rejection under 35 U.S.C. §102(e):

Claims 1-2, 7, 12, 15, 29, 33, 35, 37, 39, 41, 43, 46 and 47 stand rejected under 35 U.S.C. §102(e) as anticipated by Spitler. In particular, the Office asserts that Spitler discloses the combination of a non-DNA adjuvant and an antigen-encoding nucleic acid sequence. Applicants strongly disagree.

The Office asserts that when claims 1 and 5-7 of Spitler are read, "there can be no doubt that contemplated applicants' claimed combination of nucleic acid encoding an antigen and non-DNA adjuvant." Office Action at page 8. This is an incorrect conclusion. The subject claims of Spitler are drafted in such a way so as to cover the

various vaccine compositions that are disclosed in the Spitler specification (one cannot claim what one has not disclosed). The Office has interpreted the Spitler claims in such a way as to arrive at applicants' recited compositions, but the Office has not used the Spitler specification in order to make this interpretation, it has used applicants' specification instead. This is not permissible. One must consider the Spitler specification for what it actually disclosed to skilled artisan, where that disclosure is considered in light of the general understanding in the art at the time of applicants' filing date.

As applicants have already demonstrated in their previous response, Spitler et al. contemplated certain peptide-based vaccine compositions, and then contemplated certain DNA-based vaccine compositions. Reading the disclosure of Spitler's columns 7-8 in order (starting at the top of column 7 and ending at the bottom of column 8, one sees that Spitler et al. first considered the peptide vaccines. Next, Spitler states that liposomal compositions are preferred (generally). Spitler then switches to a specific discussion of just a certain embodiment of their invention, where liposomal formulations incorporating the prostate antigens (that is, protein antigens) may also include adjuvants. See column 7, line 47 through column 8, line 2 of Spitler. Never once does Spitler mention, suggest, describe or even so much as hint that a DNA vaccine composition may contain an adjuvant. The reason for this was simple. This combination would not have made sense to Spitler et al., nor to any other ordinarily skilled artisan without access to applicants' disclosure. This is because the skilled artisan knew and understood that for a DNA vaccine to work, the subject nucleic acid had to both gain entry into a suitable host cell cytoplasm and gain entry into the host cell nucleus where DNA could then be transcribed. Failure to get the DNA all the way into the nucleus meant failure of the vaccine since no antigen would be expressed. However, at the same time, the skilled artisan knew and

understood that adjuvants exerted their effect in the extracellular spaces of tissue. That is, lipids, proteins, saponins, alum salts and the like would not be expected to have the desired adjuvant effect if they were delivered into the nucleus of a cell. What use would it be to deliver alum into a cell nucleus? The lipid compositions described by Spitler would not be expected, for example, to be smart enough to spit out the adjuvant component prior to entry into the cell and cell nucleus, after which it would then spit out the DNA component. Accordingly, without the benefit of applicants' teaching, the skilled artisan would not combine the DNA vaccine with a non-DNA form adjuvant in a liposome as suggested by the Office. This is why when Spitler et al. discuss incorporation of adjuvants in a liposome composition, they were very careful to limit their discussion to compositions containing the prostate antigen (in protein form).

What the Office has done is to combine applicants' disclosure with the Spitler disclosure and then arrive at applicants' recited invention. When the Spitler claims are read in light of the Spitler disclosure and in light of the knowledge and understanding of the skilled artisan--without benefit of applicants' disclosure--it is clear that Spitler never contemplated combining a DNA vaccine with a non-DNA adjuvant. Claim 1 of Spitler provides two choices, protein or DNA vaccine compositions. Claim 5 of Spitler picks up certain optional compositions that contain an adjuvant. The correct reading of the Spitler specification teaches that these certain optional, adjuvant-containing compositions are always protein antigen vaccines, not DNA vaccines. Claims 6 and 7 of Spitler merely recite particular adjuvants. The Office's attention is drawn to the fact that the list of adjuvants recited in claim 7 of Spitler are taken from the Spitler specification that specifically recites that when the vaccine contains a protein antigen, they can be combined with certain adjuvants (column 7, line 47 through column 8, line 2 of Spitler).

Anticipation of a claim under §102 *requires* that each and every element of the claims be inherent in, or disclosed expressly by the anticipating reference. *Constant v. Advanced Micro-Devices, Inc.*, 7 USPQ2d 1057, 1064 (Fed. Cir. 1988). Exclusion of a single claimed element from a prior art reference is enough to negate anticipation by that reference. *Atlas Powder Co. v E.I. du Pont De Nemours & Co.* 224 USPQ 409, 411 (Fed. Cir. 1984). Further, anticipation basically requires identity with the prior art document *(Tyler Refrigeration v. Kysor Indus. Corp.*, 227 USPQ 845 (Fed. Cir. 1985)), where the identical invention must be shown in as complete detail as is contained in the rejected claim (*Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913 (Fed. Cir. 1989)). Finally, in order to anticipate, a prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public. *Akzo N.V. v. United States ITC*, 1 USPQ2d 1241 (Fed. Cir. 1986).

Spitler clearly fails to anticipate applicants' recited invention since it does not provide any disclosure whatsoever regarding applicants' recited combination of nucleic acid and non-DNA components. Since Spitler never even contemplated such a combination, the reference cannot be considered to be enabling, thus placing the allegedly disclosed matter in the possession of the public. Applicants submit that the Office's rejection is based upon an incorrect reading of Spitler, where portions of the specification dealing with peptide/protein antigen compositions has been incorrectly combined with other sections of the specification that deal with DNA compositions that encode an antigen. The only way to arrive at the Office's proposed interpretation of Spitler is to use applicants' disclosure as prior art. This is clearly not permissible.

For all of the foregoing reasons, then, the rejection of claims1-2, 7, 12, 15, 29, 33, 35, 37, 39, 41, 43, 46 and 47 under 35 U.S.C. §102(e) is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

The Rejection under 35 U.S.C. §103(a):

Claims 1, 3-5, 17-25, 29-34, 36-38, 40, 42 and 42-45 stand were rejected under 35 U.S.C. §103(a) as unpatentable over Spitler in view of Fynan, Golding and Sedegah. In particular, the Office relies upon Spitler as the primary reference for the same reasons as discussed in the Section 102 rejection, and then combines this with the secondary references to find gene gun delivery techniques (Fynan), use of a malaria antigen (Sedegah) and use MPL as an immune shift adjuvant (Golding). The Office again asserts that claims 1 and 5-7 of Spilter "clearly recite the combination of an expression system encoding PSA antigen and a non-adjuvant such as MPL." Office Action at Page 10. Applicants respectfully traverse.

Section 2143 of the M.P.E.P. sets forth the following three basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify or combine the references; (2) there must be a reasonable expectation of success for the modification and/or combination; and (3) the prior art reference must teach or suggest all the claim limitations. When assessing these issues, (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight; and (4) a reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicants submit that the Office has failed to satisfy these criteria, and has thus failed to establish *prima facie* obviousness over its proposed combination.

More particularly, as demonstrated above, the primary reference (Spitler) fails to teach or even so much as suggest that a non-DNA adjuvant should be combined with, e.g., a DNA encoding antigen in a single composition. The Spitler claims that the Office has relied upon must be read in light of both the specification and the general knowledge and skill in the art. In addition, applicants' disclosure does not form part of the prior art, and the Office cannot depend upon applicants' own teaching in order to support its' rejection.

As demonstrated herein above, Spitler carefully taught the skilled person that adjuvants could be added to certain compositions, when the antigen was in the protein form. This is exactly in line with the knowledge and skill possessed by the ordinarily skilled artisan who would not have combined a DNA vaccine with a non-DNA adjuvant in a liposome as suggested by the Office due to the expectation that these two components must be delivered to entirely different areas in order to exert their desired effect. The Office has taken applicants' disclosure and then used it to interpret the Spitler claims and disclosure in such a way that Spitler et al. never intended and in fact were careful to exclude. This is an impermissible hindsight reconstruction of the prior art, and is not properly based on the cited prior art. Applicants note that when a modification to (or combination of) a prior art disclosure would render that prior art inoperative (based on the understanding of the ordinarily skilled artisan), such a modification is improper.

Accordingly the Office's assertion that Spitler et al. somehow teach a DNA vaccine composition combined with a non-DNA adjuvant is not based on a proper reading of the Spitler claims and disclosure. It is based in its entirety on applicants' own disclosure. The secondary references to Fynan, Golding and Sedegah likewise fail to teach such a novel combination, and the Office has not asserted otherwise. Accordingly, the rejection fails to teach or suggest all of applicants' recited claim

limitations. Since the cited prior art fails to teach or suggest applicants' recited combination compositions, there cannot have been a reasonable expectation for success for such compositions. Accordingly, the Office has failed to establish a *prima facie* showing of obviousness over its proposed combination since the proposed combination and each component thereof fails to teach or suggest all of applicants' recited claim limitations. Accordingly, the rejection of claims 1, 3-5, 17-25, 29-34, 36-38, 40, 42 and 42-45 under 35 U.S.C. §103(a) is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

## CONCLUSION

Applicants respectfully submit that the claims as now pending define an invention which complies with the requirements of 35 U.S.C. § 112 and which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect is earnestly solicited. Applicants further ask that, should the Examiner note any minor remaining issues that may be resolved with a telephone call, that he contact the undersigned in the UK at +44 1865 332 600.

Respectfully submitted,

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